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| EXAMINER | |
|---|---|
| DEVI, SARVAMANGALA J N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/360,934 | COVACCI ET AL. | |
| | Examiner | Art Unit | |
| | S. Devi, Ph.D. | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *26 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40,54,61-65,72-75,82-86,93 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40, 54, 61-65, 72-75, 82-86, 93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## RESPONSE TO APPLICANTS' AMENDMENT

### Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 11/26/03 in response to the non-final Office Action mailed 06/09/03. With this, Applicants have amended the specification.

### Status of Claims

2) Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 have been amended via the amendment filed 11/26/03.

Claims 95, 96 and 98-101 have been canceled via the amendment filed 11/26/03.

Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are pending and are under examination.

### Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

### Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

### Objection(s) Withdrawn

5) The objection to the informal drawings made by the previous Examiner of record in paragraphs 3 and 4 of the Office Action mailed 12/18/02 is withdrawn in light of Applicants' submission of formal drawings filed 11/26/03.

6) The objection to the specification made in paragraph 9 of the Office Action mailed 06/09/03 is withdrawn in light of Applicants' amendments to the specification.

### Rejection(s) Moot

7) The provisional rejection of claims 95, 96 and 98-101 made in paragraph 10 of the Office Action mailed 06/09/03 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38, 44, 45 and 46 of the co-pending application SN 09/921,157, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claim 98 made in paragraph 17(a) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claims 99-101 made in paragraph 17(b) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claim 99 made in paragraph 17(c) of the Office Action mailed 06/09/03 under 35

U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

**11)** The rejection of claim 95 made in paragraph 17(d) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

**12)** The rejection of claims 95 and 99 made in paragraph 17(e) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

**13)** The rejection of claims 93 and 94 made in paragraph 17(f) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

**14)** The rejection of claims 96, 98, 100 and 101 made in paragraph 17(g) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

**15)** The rejection of claims 95, 96 and 98-101 made in paragraph 18 of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claims.

**16)** The rejection of claims 95, 96 and 98-101 made in paragraph 19 of the Office Action mailed 06/09/03 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is moot in light of Applicants' cancellation of the claims.

**17)** The rejection of claims 95, 96 and 98-101 made in paragraph 20 of the Office Action mailed 06/09/03 under 35 U.S.C. § 102(e) as being anticipated by Cover *et al.* (US 6,054,132, filed 02/26/1992 - already of record), is moot in light of Applicants' cancellation of the claims.

**18)** The rejection of claims 95, 96 and 98-101 made in paragraph 21 of the Office Action mailed 06/09/03 under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 - Applicants' IDS) (Cover *et al.*, 1992), is moot in light of Applicants' cancellation of the claims.

**Rejection(s) Withdrawn**

**19)** The rejection of claims 40, 54, 74 and 75 made in paragraph 17(a) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

**20)** The rejection of claims 63, 64, 65 and 84-86 made in paragraph 17(b) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

**21)** The rejection of claims 61, 62, 72, 73, 82 and 83 made in paragraph 17(f) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of

Applicants' amendment to the claims.

**Rejection(s) Maintained**

**22)** The provisional rejection of claims 40, 54, 63-65, 74, 75, 84 and 85 made in paragraph 10 of the Office Action mailed 06/09/03 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38, 44, 45 and 46 of the co-pending application SN 09/921,157, is maintained for reasons set forth therein. Applicants assure the Office that they would submit a terminal disclaimer over SN 09/921,157 upon the receipt of an indication of allowability.

**23)** The rejection of claims 40, 74 and 84 made in paragraph 17(c) of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants point to MPEP 2173.05 (b) and contend that the term 'substantially' often is used in conjunction with another term to describe a particular characteristic of a claimed invention. Applicants cite case law and state that definiteness will be found for use of the term 'substantially' where there are general guidelines in the specification, or where one of ordinary skill in the art would understand the meaning of the term. Applicants assert that both of these instances occur in the present case. Applicants point to the previous Del Giudice declaration and restate that one of ordinary skill in the art would understand the use of the term 'substantially' in the recited phrase to mean that the polypeptide or fragment being described does not exhibit statistically significant cytotoxic effects. Applicants further state the following:

> Moreover, the specification provides very clear guidance as to the meaning of the term "substantially" as used in the specification. For example, at page 16, lines 19-29, the term "purified" and "isolated" are defined as "substantial absence of other biological macromolecules of the same type" – i.e., "at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type". In other words, substantially pure means at least 75% pure. *Similarly*, "substantially no toxicity or a substantially reduced toxicity" means at least a 75% reduction in toxicity. [Emphasis added].

Applicants further state that the terms 'toxin' and 'cytotoxin' and 'derivatives thereof' are used interchangeably in the specification. Applicants point to page 5, line 31 to page 6, line 11 and state that 'cytotoxin' and 'toxin' are defined synonymously in the specification. Applicants contend that the 140 kDa protein set forth in Figure 2 is the precursor protein to the 100 kDa polypeptide having cytotoxic (i.e., vacuolating) activity.

Applicants' arguments have been carefully considered, but are non-persuasive. The Del Giudice declaration has been fully addressed by the Office previously. The term 'substantially' in the instant claims is not associated with 'purity', but with 'toxicity', including the intrinsic toxicity. A description provided for the term 'purified' and 'isolated' cannot and does not constitute the definition for the term 'substantially no toxicity' or 'a substantially reduced toxicity'. It is important to note that the polypeptide in the currently

claimed composition is neither an 'isolated' nor a 'purified' polypeptide. *Arguendo*, even if one equates the description for the terms 'isolated' and 'purified' with the term 'substantially no toxicity' or 'a substantially reduced toxicity', it is unclear how a substantial absence of other biological macromolecules 'of the same type' by at least 75% by weight can render the instantly claimed product a product of 'substantially no toxicity' or a product of 'substantially reduced toxicity'. As set forth previously, the term 'toxicity' encompasses cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity, or any other type of general or specific toxicity. The paragraph bridging pages 5 and 6 of the specification describes a 'cytotoxin' or 'toxin' of *H. pylori* which causes 'vacuolation and death of a number of eukaryotic cell types', but not a recombinant cytotoxin of SEQ ID NO: 3 or a fragment thereof the recited length which is of 'substantially no toxicity' or of 'substantially reduced toxicity'. A cytotoxin that causes the death of a number of eukaryotic cells cannot be viewed as being equivalent to a recombinant cytotoxin having a substantial absence of other biological macromolecules 'of the same type' by at least 75% by weight. Thus, contrary to Applicants' assertion, there are no general guidelines in the specification with regard to this issue, and therefore, one of ordinary skill in the art would not understand the meaning or the scope of the phrase. The only place where the phrases were mentioned in the specification as originally filed was in some original claims. There appears to be no general guidelines or definition for these phrases in the specification for one to understand the meaning or scope of the phrases, or the difference between the two phrases.

**24)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 18 of the Office Action mailed 06/09/03 under 35 U.S.C. § 112, first paragraph, as containing new matter, is maintained for reasons set forth therein and herebelow.

Applicants contend that support for the limitations 'immunologically identifiable by antibodies, which react specifically with the polypeptide having the amino acid sequence of SEQ ID N: 3' is found throughout the specification as filed. Applicants point to lines 18-20 of page 15 and page 45, line 26 to page 46, line 6 and state that the specification discloses the preparation of antisera against the *Helicobacter pylori* cytotoxin and the use of the antisera to specifically detect polypeptides immunologically identifiable with the *H. pylori* cytotoxin.

Applicants' arguments have been carefully considered, but are non-persuasive. What is claimed in the instant claims is a recombinant polypeptide of any length, including a five-mer, a ten-mer, a fifteen-mer etc., from the amino acid sequence of SEQ ID NO: 3, which while exhibiting substantially no toxicity or substantially reduced toxicity, is also 'immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3'. The parts of the specification pointed to by Applicants do not support such a recombinant five-mer, ten-mer, fifteen-mer etc. or a recombinant polypeptide of SEQ ID NO: 3 being immunologically identified by 'antibodies that react specifically with the

polypeptide having the amino acid sequence of SEQ ID NO: 3'. On the other hand, the specific parts of the specification describe rabbit antisera containing antibodies raised using a partially purified fusion protein that comprises the amino acids of the 'cytotoxin' polypeptide encoded by nucleotides 116-413 of the nucleotide sequence shown in Figure 1 (SEQ ID NO: 2). There is no descriptive support that this particular fragment in the fusion protein exhibits substantially no toxicity of any kind including cytotoxicity, or exhibits substantially reduced toxicity of any kind, including cytotoxicity. The antisera thus produced using a specific fragment of SEQ ID NO: 3 encoded by nucleotides 116-413 of the nucleotide sequence shown in Figure 1 (SEQ ID NO: 2) is used to 'probe protein extracts from a cytotoxin positive and a cytotoxin negative strain' of *H. pylori* by immunoblotting. The antisera detected a polypeptide in the protein extracts of the 'cytotoxin positive' strain, the amino acid sequence of which polypeptide is unknown. The polypeptide identified by the antisera is a non-recombinant polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori,* whose amino acid sequence is not described as being SEQ ID NO: 3. A non-recombinant polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori* is expected to be fully cytotoxic, as opposed to be substantially non-cytotoxic. Therefore, the description in pages 45 and 46 does not and cannot provide support for a 'recombinant' polypeptide that is a five-mer, ten-mer, fifteen-mer etc. from SEQ ID NO: 3, or even a full length 'recombinant' polypeptide that exhibits substantially no toxicity, or substantially reduced toxicity and which is also immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. There is no descriptive support for a single non-toxic or non-cytotoxic recombinant five-mer, decamer, fifteen-mer, twenty-mer polypeptide etc. from SEQ ID NO: 3 that is also immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. The rejection stands.

**25)** The rejection of claims 40, 54, 61-65, 72-75, 82-85, 93 and 94 made in paragraph 19 of the Office Action mailed 06/09/03 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is maintained for reasons set forth therein and herebelow.

Applicants contend that the specification discloses functional information, i.e., the characteristics of being immunologically identifiable by antibodies that react specifically with the polypeptide of SEQ ID NO: 3, or with the polypeptide encoded by SEQ ID NO: 2, and exhibiting substantially no toxicity or substantially reduced toxicity, and the structural information, i.e., a recombinant polypeptide comprising at least a fragment of the amino acid sequence of SEQ ID NO: 3, for the skilled artisan to correlate the function with a known structure. Applicants acknowledge that the *H. pylori* cytotoxin described at page 5, lines 35-39 and page 46, lines 7-29, 'causes formation of vacuoles in eukaryotic cells'. Applicants state that the claimed recombinant polypeptide, however, exhibits substantially no toxicity, or substantially reduced toxicity.

Applicants submit that the claimed polypeptide, for example, 'may be' a genetically or chemically detoxified form of the cytotoxin, or a fragment of the native cytotoxin, having no toxicity. Applicants further state that the claimed polypeptide 'may' exhibit substantially no toxicity or substantially reduced toxicity by virtue of being recombinantly produced. Applicants then cite the post-filing publication of Manetti *et al.* (*Infect. Immun.* 63: 4476-4480, 1995) and state that the recombinantly produced '95 kDa polypeptide' taught by Manetti *et al.* indeed lacks toxicity, while being immunogenic. Applicants further cite yet another post-filing reference of Ghiara *et al.* (*Infect. Immun.* 65: 4996-5002, 1997), but provide no explanation as to its relevance to the instant rejection. Applicants mention about the Del Giudice Declaration, which allegedly stated that it would have been routine to determine cytotoxin fragments that exhibit substantially no toxicity or substantially reduced toxicity. Applicants further point to the specification at page 45, line 25 to page 46, line 6 as describing the claimed polypeptide.

Applicants' arguments have been carefully considered, but are non-persuasive. It is noted that what is claimed in the instant claims is a recombinant *H. pylori* (cytotoxin) polypeptide which "exhibits substantially no toxicity", "substantially reduced toxicity". What is claimed is not a structurally distinct pertussis toxin subunit that is detoxified recombinantly. The instant specification does provide sufficient functional and structural characteristics of a fully cytotoxic polypeptide of *H. pylori* that has the amino acid sequence of SEQ ID NO: 3. The paragraph bridging pages 5 and 6 of the specification describes the molecular weight and the ability of such a *H. pylori* cytotoxin to cause 'vacuolation and death of a number of eukaryotic cell types'. The paragraph bridging pages 45 and 46 describes the immunological reactivity of protein extracts from 'cytotoxin positive' strains of *H. pylori*. See paragraph above for a detailed rebuttal with regard to what is and what is not disclosed in this part of the specification. There are no non-cytotoxic or less cytotoxic recombinant polypeptides of SEQ ID NO: 3, or five-mer, ten-mer or fifteen-mer fragments thereof described therein, which at the same time show the specific immunological reactivity as recited. A chemically detoxified form of the cytotoxin does not qualify as a 'recombinant' polypeptide. A fragment of the 'native' cytotoxin does not qualify as a 'recombinant' polypeptide. A genetically 'detoxified' form of the cytotoxin, a five-mer, a ten-mer or a fifteen-mer thereof, having the recited function(s) is not described within the instant specification as originally filed, let alone how to make such a product such that it retains its immunological specificity. Applicants never had possession of a genetically detoxified form of the cytotoxin of *H. pylori* having the full or partial structure of SEQ ID NO: 3 that had the recited immunological property or specificity. At the time of the instant invention, it was not known in the art how to produce a detoxified recombinant *H. pylori* cytotoxin of SEQ ID NO: 3, or an at least 5-mer, 10-mer or fifteen-mer detoxified fragment thereof, such that it retained the ability to be immunologically identifiable by antibodies reactive specifically with the polypeptide of the amino acid sequence, SEQ ID NO: 3. Therefore, those of skill in the

art could not have envisioned the structure of the claimed polypeptide commensurate in scope with the recited functions. With regard Applicants' citation of Manetti *et al.*, Manetti's post-filing disclosure of a 95 kDa *H. pylori* cytotoxin does not and cannot provide adequate description for a recombinant 87 kDa, 100 kDa, or 140 kDa cytotoxin of *H. pylori* of the instant invention, or fragments thereof as claimed. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc., v. Novo Nordisk A/S Ltd., 42 USPQd 1001*. Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright, 27 USPQ2d 1510*). A review of the second post-filing reference mentioned by Applicants, Ghiara *et al.* (*Infect. Immun.* 65: 4996-5002, 1997), indicates that this reference has nothing to do with the claimed cytotoxin of SEQ ID NO: 3.

The genetic detoxification alluded to in the Del Giudice Declaration was not contemplated in the instant specification, as originally filed. Nowhere in the specification can one find the direction and guidance to produce detoxified cytotoxins of *Helicobacter pylori,* or their fragments of the recited length, such that they possess substantial non-cytotoxicity, or substantially reduced cytotoxicity and at the same time remain immunologically identifiable by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin of SEQ ID NO: 3. The Del Giudice Declaration discusses pertussis toxin, which has a structure distinct from the instantly claimed product. Further, the Declaration does not address the 'unpredictability' factor. The teaching in the specification is contrary to this. For example, at page 7, lines 33-37, the specification teaches polypeptide molecules having amino acid substitutions 'that do not substantially affect the functional aspects', i.e., cytotoxin polypeptides having amino acid substitutions such that their cytotoxic activity remains substantially the same as the native polypeptide. Therefore, using the application as a guide, one of ordinary skill in the art would have been able to produce *Helicobacter pylori* cytotoxin polypeptides that retain substantial cytotoxicity. The specification, for example, in the second paragraph on page 7, mentions of conservative amino acid replacement and states that 'it is reasonably predictable that an isolated replacement of a leucine with isoleucine ... or a similar conservative replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological activity'. The biological activity includes cytotoxicity. There is no disclosure as to which amino acids at which positions can be substituted such that one can obtain the recombinant polypeptide, or a five-mer, ten-mer, or a fifteen-mer fragment thereof that has the recited immunological specificity along with substantial non-toxicity. Therefore, it is reasonable to conclude that the retention of immunologic identifiability concurrently with the substantial attenuation of cytotoxicity of a cytotoxin has not been demonstrated and is not predictable without a clear showing, and would have required a considerable amount of undue experimentation. The specification

recites therapeutic, prophylactic and diagnostic applications or vaccine intentions for the claimed polypeptide products. However, the instant specification fails to teach such non-cytotoxic polypeptides, which concurrently have the ability to bind to a SEQ ID NO. 3-specific antibody. Diagnostic or vaccine applications minimally require an ability to elicit a specific immune response or bind specifically to a specific antibody. The precise structure or relevant identifying characteristics of each DNA molecule that encodes a recombinant polypeptide fragment of SEQ ID NO: 3 having the specific binding ability and non-cytotoxicity can only be determined empirically by actually making every DNA molecule that encodes the polypeptide fragment, and testing each varied DNA molecule to determine whether it encodes the recited polypeptide fragment having the particularly disclosed specific binding activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

The Manetti's post-filing publication in fact provides the *prima facie* evidence that in 1995, about three years after the effective filing date of the instant invention, there was no predictability in obtaining the claimed detoxified *Helicobacter pylori* cytotoxin polypeptide fragments that are conformationally competent and therefore immunolgically functional. Mannetti *et al.* taught the conformational complexity of a *Helicobacter pylori* cytotoxin polypeptide. Manetti *et al.* also taught that the immune response is primarily due to conformational epitopes. Manetti *et al.* specifically taught that "[e]ven partial destruction of the conformational epitopes by chemical inactivation can result in lowering of the effective immunogenicity". With regard to the genetic detoxification, Manetti *et al.*, in 1995, stated that a "genetically detoxified molecule which retains the native structure **will be** an important goal" (see page 4479), thus indicating that genetic detoxification of *Helicobacter pylori* cytotoxin was not achieved at least until 1995. Manetti's reference in fact supports the Office's position by establishing that, in 1995, a *Helicobacter pylori* cytotoxin produced recombinantly 'lacked any biological activity' and 'failed to induce neutralizing antibodies after immunization of rabbits' (see abstract of Manetti *et al.*). A recombinant cytotoxin that induces non-neutralizing antibodies would not be expected by those of skill in the art to be of any prophylactic or therapeutic value. Pizza's disclosure on pertussis toxin alluded to in the Del Giudice Declaration cannot and does not provide adequate written description for the structurally unrelated *Helicobacter pylori* cytotoxin polypeptide. Although one may be able to produce fragments of SEQ ID NO: 3 and test their cytotoxicity and immunological identifiability, given the art-disclosed conformational complexity and functional unpredictability, the maintenance of immunological identifiability by an antibody specifically reactive with

the native cytotoxin polypeptide of SEQ ID NO: 3 along with the concurrent acquisition of the recited attenuation in cytotoxic activity following one or more amino acid substitutions in the cytotoxin polypeptide, would not have been predictable, absent a concrete showing. Retention of conformational epitopes within a five-mer, ten-mer or fifteen-mer fragment of a recombinant polypeptide of SEQ ID NO: 3 such that it is immunologically reactive with an antibody specific to the native polypeptide and at the same time non-cytotoxic or substantially less cytotoxic is not a predictable event. Regardless of the complexity or simplicity of the method of isolation and method of testing, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is a part of the invention and a reference to a potential method of isolating or testing it. In light of the unpredictability disclosed in the art and the Manetti teachings published in 1995, it does not appear that Applicants were in possession of the claimed product, wherein the product is required to possess the two specific functions recited in the claims. It should be noted that the only place where the phrase 'substantially no toxicity' or 'substantially reduced toxicity' was mentioned in the specification as originally filed was in some original claims. Other than this, there is no direction and guidance as to how to produce either a full length cytotoxin of SEQ ID NO: 3 or fragments thereof, including recombinant ones, which possess the two required functions: i) substantially no cytotoxicity, or substantially reduced cytotoxicity, and ii) immunological identifiability by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin. A 100 kDa 'fragment' for example of the precursor protein is 'cytotoxic' as opposed to 'substantially non-cytotoxic' (see page 5, last paragraph). The definition for 'cytotoxin' provided in the instant specification is a non-limiting definition for a non-recombinant polypeptide, which does not exclude a processed 100 kDa polypeptide possessing cytotoxic activity.

Applicants' remarks about the specification at page 45, line 25 to page 46, line 6 have been addressed above. See paragraph 24 above.

Clearly, the evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the invention. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The rejection stands.

**26)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 20 of the Office Action mailed 06/09/03 under 35 U.S.C. § 102(e) as being anticipated by Cover *et al.* (US 6,054,132, filed 02/26/1992 - already of record), is maintained for reasons set forth therein and herebelow. See the following paragraph.

**27)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 21 of the Office Action mailed 06/09/03 under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 - Applicants' IDS) (Cover *et al.*, 1992), is maintained for reasons set forth therein and herebelow.

Applicants state that the reference of Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992) is not prior art under 35 U.S.C. § 102(b), but provide no explanation as to why the reference is not prior art under 35 U.S.C. § 102(b). Applicants cite case law and state that to anticipate a claim, a prior art reference must teach, either expressly or inherently, each and every element of the claim. Applicants contend that the '132 patent discloses the purification from *H. pylori* culture supernatant of a vacuolating toxin having a molecular weight of 87 kDa. Applicants point to Table 1 of the '132 patent and state that the prior art purification scheme resulted in a greater than 5000-fold increase in specific activity of the toxin measured as a function of cell vacuolating activity. Applicants make a similar remark with regard to the teachings of Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992). With this, Applicants conclude that the '132 patent does not teach a recombinant polypeptide of the present claims possessing substantially no toxicity or substantially reduced toxicity.

Applicants' arguments have been carefully considered, but are non-persuasive. Because of the new matter identified via paragraph 18 of the Office Action mailed 06/09/03, instant claims do not get priority to earlier applications. Therefore, the reference of Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992) is properly applied under 35 U.S.C. § 102(b).

As set forth previously, Cover *et al.* ('132) disclosed an antigenic polypeptide of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori* which is recombinantly or synthetically produced, and a composition comprising the same (see column 2, lines 25-58). The polypeptide comprises a 23 amino acid-long N terminus of the toxin antigen, i.e., SEQ ID NO: 1, and is obtained from the purified polypeptide (see column 10, lines 2-4; and first sequence in columns 17 and 18 under Sequence Listing). The 23 amino acid-long antigenic portion of the polypeptide of the prior art has 100% sequence or structural identity with a 23 amino acid-long contiguous portion that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3. The antigenic polypeptide is present along with water, phosphate buffered saline or an adjuvant (see column 18, third paragraph; column 17, second paragraph; and column 16, lines 45-50). The polypeptide has a molecular weight of 87,000 or 972,000 daltons (see column 2, seventh full paragraph). That the structurally identical 23 amino acid-long antigenic polypeptide of the prior art obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or of substantially reduced LPS-related toxicity, and is long enough to be immunologically identifiable by antibodies specific to the amino acid sequence of SEQ ID NO: 3 are inherent from the teachings of Cover *et al.* ('132). Given that the structural elements of the instant

claims are met by the prior art antigenic polypeptide, the immunological identifiability by antibodies specifically reactive with the amino acid sequence of SEQ ID NO: 3 and/or the exhibition of substantially no toxicity or of substantially reduced toxicity, including cytotoxicity, are viewed as the inherent properties inseparable from the antigenic polypeptide taught by Cover *et al.* ('132).

Similarly, Cover *et al.* (1992) disclosed a polypeptide comprising an antigenic N-terminal portion of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori,* which is recombinantly or synthetically produced and a composition comprising the same in distilled water (see Table III and page 10571, left column). This polypeptide comprising the 23 amino acid-long portion is obtained from the purified toxin antigen and has 100% sequence identity with a 23 amino acid-long contiguous polypeptide portion that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3. The polypeptide has a molecular weight of 87,000, or 972,000 daltons (see page 10573, right column; and page 10574, left column). That the polypeptide comprising the 23 amino acid-long antigenic portion of the prior art, obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or exhibits substantially reduced contribution to LPS-related toxicity, and is long enough to be immunologically identifiable by an *H. pylori*-specific antibody are inherent from the teachings of Cover *et al.* Given that all the structural elements of the instant claims are met by the prior art antigenic polypeptide, the immunological identifiability by an antibody specifically reactive with *H. pylori* cytotoxin and the exhibition of substantially no toxicity, or of substantially reduced toxicity, including cytotoxicity, are viewed as the inherent or intrinsic properties inseparable from the antigenic polypeptide taught by Cover *et al.* (1992).

The prior art polypeptide is structurally identical to the instantly claimed polypeptide, irrespective of how it is obtained. Furthermore, the term "recombinant" and/or "expressed from ..... nucleotides of SEQ ID NO: 2" in some of the claims represent process limitations. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art antigenic polypeptide differs from that of

the instantly claimed antigen of the amino acid sequence of SEQ ID NO: 3.

Contrary to Applicants' assertion, there is no indication or disclosure in the '132 patent and the Cover's 1992 reference to demonstrate that the prior art purification scheme resulted in a greater than 5000-fold increase in the toxicity of their 23 amino acid-long polypeptide that shows 100% sequence identity with the instantly claimed polypeptide fragment. Furthermore, with regard to Cover *et al.* (1992), it is important to note Applicants' admission within the instant specification. In the first part of page 6 of the specification, Applicants cite Cover *et al.* (1992) and state that 'the previously described 87 kDa results from either the further processing of the 100 kDa protein or from proteolytic degradation of a larger protein during purification'. See also lines 27-30 on page 47 of the specification. The fourth full paragraph on page 45 of Applicants' specification acknowledges that the amino acid fragment encoded by the nucleotides 116-413 of the sequence shown in Figure 1 (i.e., SEQ ID NO: 2) and fused to a part of the MS2 polypeptide includes 'the 23 amino acids previously identified'. The specification at lines 10-14 of page 47 readily admits that this 23 amino acid-long sequence is identified as 'the amino terminus of the previously described 87 kDa vacuolating protein, .....J. Biol. Chem. 267: 10570-75 (1992)'. It is noteworthy that what is claimed in the instant claim 61 encompasses the 87 kDa polypeptide.

The Office has met the burden and the art rejections stand.

**Remarks**

**28)** Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 stand rejected.

**29)** **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

**30)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

**31)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

February, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER